

# PATENT SPECIFICATION

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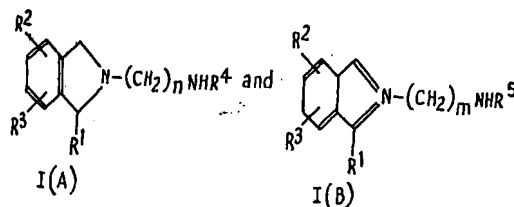
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## (54) ISOINDOLES AND ISOINDOLINES

(71) We, AMERICAN HOME PRODUCTS CORPORATION, a corporation organised and existing under the laws of the State of Delaware, United States of America, of 685, Third Avenue, New York City 17, New York, United States of America, do hereby declare the invention for which we pray that a patent may be granted to us and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to new isoindoles and isoindolines to processes for the preparation thereof, and to pharmaceutical compositions containing them.

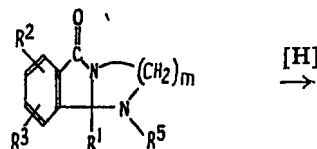
In particular, the present invention is concerned with novel 2-(aminoalkyl)isoindolines and 2-(aminoalkyl)isoindoles of the general formulae



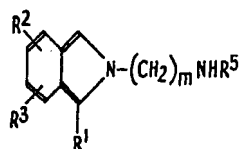
and their pharmaceutically acceptable acid addition salts, in which formulae  $R^1$  is lower alkyl, phenyl, phen(lower)alkyl, monohalophenyl e.g. monochlorophenyl, dihalophenyl e.g. dichlorophenyl, mono(lower)alkylphenyl e.g. tolyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl, or 5,6,7,8-tetrahydro-2-naphthyl;  $R^2$  and  $R^3$  are the same and are hydrogen, halogen e.g. bromine, lower alkyl or lower alkoxy; or  $R^2$  is hydrogen and  $R^3$  is amino, loweralkylamino, halogen e.g. bromine, lower alkyl or lower alkoxy;  $R^4$  is hydrogen or toluenesulphonyl;  $R^5$  is lower alkyl,  $m$  is 2 or 3;  $n$  is an integer from 2 to 7. The term "lower" as used herein means that the radical contains up to 6, preferably up to 4 carbon atoms.

The compounds of general formula I (A) are "isoindolines" and examples of such compounds are *N*-(2-[1-(4-chlorophenyl)-2-isoindolinyl]ethyl)-4-toluenesulphonamide and *N*-(3-[1-(4-chlorophenyl)-2-isoindolinyl]propyl)-4-toluenesulphonamide. The compounds of general formula I(B), are properly called: "Isoindoles". A typical example thereof is 2-[2-(ethylamino)ethyl]-1-phenylisoindole hydrochloride. Some isoindoles in which  $R^5$  is hydrogen and  $m=3$  are described and claimed in application 45729/70 Serial No. 1229653 divided out of this application. The isoindoles may be

prepared by the reaction of a hexahydropyrimido isoindolone or a 1-alkyltetrahydroimidazoisindolone with lithium aluminum hydride as shown in the following equation:



(II)

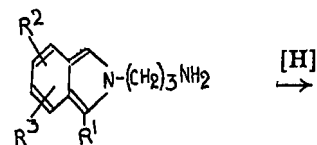


I(B)

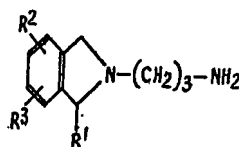
wherein  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^5$  and  $m$  have the meanings defined above. This reaction can be effected by reacting a hexahydropyrimido isoindolone or a 1-alkyltetrahydroimidazoisindolone of formula (II), in an anhydrous reaction-inert organic solvent at a temperature from  $30^\circ\text{C}$  to  $80^\circ\text{C}$  e.g. for a period of from one to seventeen hours. Preferably, the reaction is conducted in anhydrous ether at the reflux temperature of the reaction mixture e.g. for a period of about two hours. The term "anhydrous reaction-inert organic solvent" as employed herein means an anhydrous organic solvent which dissolves the reactants but does not react with them under the above described reaction conditions. Many such solvents will suggest themselves to those skilled in the art, and excellent results can be obtained with anhydrous solvents such as dioxan, ethyl ether, diisopropyl ether, ethylene glycol dimethyl ether and diethylene glycol dimethyl ether.

After the reaction is complete, the excess lithium aluminum hydride can be decomposed by the addition of water, the organic layer separated and the product obtained by conventional methods, such as concentration and crystallisation. For example, the organic layer may be dried over a desiccant and then evaporated to dryness. The residue is the desired isoindole. This product may then be dissolved in an appropriate organic solvent, such as, a lower alkanol, benzene, toluene, ethyl acetate, ether, chloroform, carbon tetrachloride or dimethyl formamide and reacted with a mineral acid to obtain the mineral acid addition salt of the particular isoindole. The starting materials of general formula (II), and their preparation, are described and claimed in our U.K. Patent No. 1,059,175.

The 2-(3-aminopropyl)isoindoline compounds falling within general formula I(A) may be prepared by the catalytic hydrogenation of a 2-(3-aminopropyl)isoindole for example as prepared above. The reaction scheme is illustrated below:



(III)



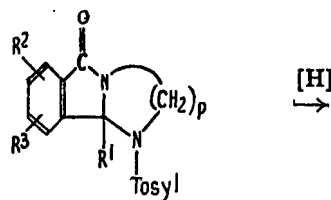
(IV)

where  $R^1$ ,  $R^2$  and  $R^3$  are as defined above. The catalytic reduction can be effected by contacting a 2-(3-aminopropyl)isoindoline with a palladium charcoal catalyst, in an

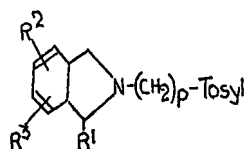
appropriate solvent, e.g. acetic acid, under a positive hydrogen atmosphere with stirring until the hydrogen uptake ceases. Preferably, this reaction is conducted with a 10% palladium on charcoal catalyst under about 45 p.s.i. of hydrogen pressure. The term "palladium charcoal catalyst" as employed above means a catalyst comprising two percent to ten percent palladium on charcoal. The term "positive atmosphere" means a hydrogen pressure of 15 p.s.i. to 75 p.s.i.

When the aforesaid catalytic hydrogenation reaction is complete, the product can be obtained by conventional procedures, for example the catalyst can be removed by filtration or decantation; the filtrate evaporated to dryness; the residue dissolved in water, basified with a base, e.g. sodium hydroxide, potassium hydroxide, sodium bicarbonate and potassium bicarbonate; extracted with a water-immiscible solvent, for example, ethyl acetate, ether, chloroform, carbon tetrachloride and benzene; and the extract evaporated to dryness to afford the appropriate 2-(3-aminopropyl)isoindole.

Furthermore, it has unexpectedly been found that when a 1-tosylhexahydropyrimido isoindolone or a 1-tosyltetrahydro imidazoisoindolone is reduced with lithium aluminum hydride the corresponding isoindolinyltoluenesulphonamide is produced. This reaction proceeds as follows:



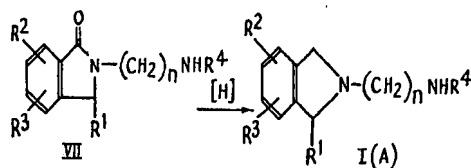
(V)



(VI)

where  $R^1$ ,  $R^2$  and  $R^3$  are as defined above and  $p$  is 2 or 3. When the reaction is complete, the resulting isoindolinyltoluenesulphonamide can be separated by standard recovery procedures, for example those given above. The 1-tosylhexahydropyrimido isoindolones and the 1-tosyltetrahydro imidazoisoindolones starting materials employed in accordance with process of the present invention can be prepared by routine organic procedures from their corresponding hexahydropyrimido isoindolones and tetrahydro imidazoisoindolones. In particular, these tosyl derivatives may be prepared by reacting a particular hexahydropyrimido isoindolone or tetrahydro imidazoisoindolone with toluenesulphonyl chloride, in pyridine, at reflux temperatures for about sixteen hours. Thereafter, the resulting tosyl derivative may be separated by standard procedures e.g. evaporation, and recrystallisation of the residue from a suitable solvent, such as, an alkanol.

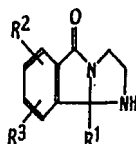
Furthermore, the 2-[aminoalkyl] and the tosyl derivatives thereof of general formula IA may be prepared by reduction of an appropriate 2-[aminoalkyl]phthalimidine or N-[phthalimidinylalkyl]-*p*-toluenesulphonamide as illustrated by the following reaction scheme:



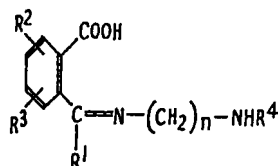
where  $R^1$ ,  $R^2$ ,  $R^3$  and  $R^4$  are as defined above. This reduction preferably is effected with lithium aluminium hydride in the same manner as set forth in the first above-

described process. When the reduction reaction is complete, the resulting isoindolone can be separated by standard procedures exemplified above.

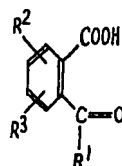
Some of the 2-[amino(lower)alkyl]phthalimidines, which are employed as starting materials in this process may be prepared by reducing a tetrahydroimidazoisoindolone of general formula



with hydrogen in the presence of a palladium charcoal catalyst, e.g. in acetic acid, (as described in United States Patent No. 3,445,476). Alternatively, the 2-[amino(lower)alkyl]phthalimidines may be prepared from an  $\alpha$ -imino-2-toluic acid of general formula



by reacting an appropriate  $\alpha$ -imino-2-toluic acid with hydrogen in the presence of palladium on carbon, e.g. at an initial pressure of about 45 p.s.i. in the presence of an above-defined "palladium charcoal catalyst" in a solvent e.g. acetic acid, an alkanol and dioxan, for a period of about two to about twenty-four hours. Thereafter, the resulting 2-[amino(lower)alkyl]phthalimidine can be separated by conventional procedures, such as, removing the catalyst by filtration and evaporating the filtrate to dryness. The  $\alpha$ -imino-2-toluic acids can be prepared by condensing a 2-carbonyl benzoic acid of general formula



with a diamine of general formula  $\text{NH}_2(\text{CH}_2)_n\text{NHR}^4$ .

The N-[phthalimidinylalkyl]-*p*-toluenesulphonamide starting materials for this process may also be prepared by reacting a 2-[aminoalkyl]phthalimidine with *p*-toluenesulphonyl chloride, for example, in pyridine at reflux temperature for a period of about two hours. When the reaction is complete, the resulting N-[phthalimidinylalkyl]-*p*-toluenesulphonamide can be obtained by routine methods, e.g. evaporation to dryness and recrystallisation of the residue from an alkanol.

Some of the N-[phthalimidinylalkyl]-*p*-toluenesulphonamides used as starting materials in this process of this invention may also be prepared by contacting an appropriate hexahydropyrimido isoindolone or a tetrahydroimidazoisoindolone tosyl derivative, as prepared above, with hydrogen at an initial pressure of about 45 p.s.i. in the presence of a palladium charcoal catalyst in a suitable solvent e.g. ethanol for a period of about twenty hours. When the reaction is complete, the resulting N-[phthalimidinylethyl]-*p*-toluenesulphonamide or N-[phthalimidinylpropyl]-*p*-toluenesulphonamide can be obtained by standard recovery procedures e.g. concentration and followed by recrystallisation of the residue from ethanol.

The time and temperature ranges utilised in the aforesaid processes are not critical and simply represent the most convenient ranges consistent with carrying out the reaction in a minimum of time without undue difficulty. Reaction temperatures appreciably below the demonstrated ranges can be used, but their use considerably extends the reaction time. Similarly, in some cases, temperatures higher than those mentioned can be employed with a proportionate decrease in reaction time.

Since the nitrogen containing compounds of the present invention are basic, ad-

vantage may be taken of the water solubility of salts of these compounds formed with acids in the isolation and/or purification of the above compounds and in the preparation of aqueous solutions of these new compounds for oral or parenteral administration. Of course, only salts formed with pharmaceutically acceptable acids should be employed in therapeutic applications. Particularly effective salts are those formed with pharmaceutically acceptable acids having a pH value of 3 or below. Such acids are well known in the art, for example, hydrochloric, hydrobromic, hydroiodic, sulphuric, nitric, phosphoric, acetic, lactic, citric, tartaric, maleic, gluconic, benzenesulphonic, toluenesulphonic, methylsulphonic and ethylsulphonic acids. These salts may be prepared by procedures commonly employed in the art, for example, reacting the compound with an equivalent of the selected acid in aqueous solution and concentration of the solution. Other known procedures may also be employed.

The isoindoles and isoindolines of general formula I(A) and I(B) have been found to possess interesting pharmaceutical properties which render them useful as synthetic medicinals. More particularly, these compounds, in standard pharmacological tests, have exhibited utility as anorexiant and anti-depressants. In addition to their pharmacological utility, the 2-(3-aminopropyl)isoindoles of the present invention may be utilised as intermediates, as they can be oxidised to the corresponding tetrahydropyrimidinyl phenyl carbonyl compounds, which latter compounds and their preparation are described and claimed in our co-pending British application No. 13421/68 Serial No. 1229652 of even date. The 2-(3-aminopropyl)isoindoles are also useful intermediates in the preparation of their corresponding 2-(3-aminopropyl)isoindolines as described herein.

When the compounds of this invention are employed as anorexiant and anti-depressants, they may be administered alone or in combination with pharmaceutically acceptable carriers, the proportion of which is determined by the solubility and chemical nature of the compound, chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk, sugar, certain types of clay and so forth. They may be administered sublingually in the form of troches or lozenges in which the active ingredient is mixed with sugar and corn syrups, flavouring agents and dyes; and then dehydrated sufficiently to make it suitable for pressing into a solid form. They may be administered orally in the form of solutions which may contain colouring and flavouring agents or they may be injected parenterally, that is intramuscularly, intravenously or subcutaneously. For parenteral administration they may be used in the form of a sterile solution containing other solutes, for example, enough saline or glucose to make the solution isotonic.

The dosage of the present therapeutic agents will vary with the form of administration and the particular compound chosen. Furthermore, it will vary with the particular subject under treatment. Generally, treatment initiated with small dosages substantially less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. It will generally be found that when the composition is administered orally, larger quantities of the active agent will be required to produce the same effect as a smaller quantity given parenterally. In general, the compounds of this invention are most desirably administered at a concentration level that will generally afford effective results without causing any harmful or deleterious side effects and preferably at a level that is in the range of from 0.1 mg. to 10 mg. per kg. of body weight per day, although as aforementioned variations will occur. However, a dosage level that is in the range of from 1.0 mg. to 4 mg. per kg. of body weight per day is most desirably employed in order to achieve effective results.

The following non-limiting Examples illustrate the invention:—

#### EXAMPLE 1

Fifteen grams of 10b-(4-chlorophenyl)-1,2,3,4,6,10b-hexahydropyrimido[2,1- $\alpha$ ]isoindol-6-one were slowly added to a stirred suspension of 4 grams of lithium aluminum hydride and 250 ml. of anhydrous ether. The mixture was then refluxed with stirring for two hours. Thereafter, the excess hydride was decomposed by careful addition of water and the ether layer separated, dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in 50 ml. of ethanol and saturated with anhydrous hydrogen chloride. The mixture was cooled and the solid separated by filtration. After recrystallisation from aqueous ethanol, 2-(3-aminopropyl)-1-(4-chlorophenyl)isoindole, hydrochloride, m.p. 265°C (dec) was obtained. Anal. Calcd. for  $C_{17}H_{17}ClN_2.HCl$ : C, 63.55; H, 5.65; N, 8.72; Cl, 22.07. Found: C, 63.31; H, 5.39; N, 8.62; Cl, 22.00.

Ten grams of 2-(3-aminopropyl)-1-(4-chlorophenyl)isoindole hydrochloride, as prepared as above, 3 g. of 10% palladium charcoal and 125 ml. of glacial acetic acid were shaken with hydrogen at an initial pressure of 43 p.s.i. One equivalent of hydrogen was absorbed with forty five minutes and the hydrogen uptake then ceased. The catalyst was separated by filtration and the filtrate evaporated to dryness *in vacuo*. On recrystallisation of the residue from ethanol 2-(3-aminopropyl)-1-(4-chlorophenyl)isoindoline hydrochloride, m.p. 245—7°C was obtained.

Anal. Calcd. for  $C_{11}H_{10}ClN_2$ : C, 63.16; H, 6.23; N, 8.66; Cl, 21.94. Found: C, 63.18; H, 6.11; N, 8.52; Cl, 22.0.

#### EXAMPLE 2

The procedure of Example 1 can be repeated reacting an appropriate pyrimidoisoindolone with lithium aluminum hydride to produce the 2-(3-aminopropyl)isoindoles listed below. When these isoindole compounds are hydrogenated by the procedure of Example 2, the hereinafter listed products are obtained:

15	2-(3-AMINOPROPYL)ISOINDOLES	PRODUCTS	15
	2-(3-aminopropyl)-6-bromo-1-(4-tolyl)isoindole	2-(3-aminopropyl)-6-bromo-1-(4-tolyl)isoindoline	
	2-(3-aminopropyl)-5-methyl-1-propylisoindole	2-(3-aminopropyl)-5-methyl-1-propylisoindoline	
20	2-(3-aminopropyl)-1-(4-bromophenyl)-5,6-dibromoisindole	2-(3-aminopropyl)-1-(4-bromophenyl)-5,6-dibromoisindoline	20

#### EXAMPLE 3

Following the procedure of Example 1, twenty two grams of 10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido [2,1-a]isoindol-6-one were reduced with lithium aluminum hydride to 2-(3-aminopropyl)-1-phenylisoindole. The crude isoindole, 3 g. of 10% palladium on charcoal and 125 ml. of glacial acetic acid were shaken with hydrogen at an initial pressure of 40 p.s.i. for one hour. Thereafter, the mixture was filtered and the filtrate evaporated to dryness. On recrystallisation of the residue from ethyl acetate-ethanol, there was obtained 2-(3-aminopropyl)-1-phenylisoindoline acetate, m.p. 147—9°C.

Anal. Calcd. for  $C_{17}H_{20}N_2$ : C, 73.05; H, 7.74; N, 8.97. Found: C, 72.93; H, 7.46; N, 8.68.

In a similar manner, starting with 10b-(3,4-dichlorophenyl)-1,2,3,4,6,10b-hexahydropyrimido [2,1-a]isoindol-6-one 2-(3-aminopropyl)-1-(3,4-dichlorophenyl)isoindoline acetate, m.p. 135—7°C. was obtained.

Anal. Calcd. for  $C_{17}H_{16}Cl_2N_2$ : C, 59.85; H, 5.82; N, 7.34; Cl, 18.60. Found: C, 59.77; H, 5.66; N, 7.58; Cl, 18.40.

#### EXAMPLE 4

Following the procedure of Example 1, 10b-(4-trifluoromethylphenyl)-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one was first reduced with lithium aluminum hydride to 2-(3-aminopropyl)-1-(4-trifluoromethylphenyl)isoindole. Thereafter, the isoindole, 3 g. of 10% palladium on charcoal and 125 ml. of glacial acetic acid were shaken with hydrogen for one hour to afford 2-(3-aminopropyl)-1-(4-trifluoromethylphenyl)isoindoline acetate, m.p. 168—170°C.

Anal. Calcd. for  $C_{18}H_{16}F_3N_2$ : C, 63.10; H, 6.10; N, 7.37. Found: C, 63.16; H, 6.01; N, 7.24.

#### EXAMPLE 5

Five grams of 10b-(4-bromophenyl)-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one were slowly admixed with 1.3 grams of lithium aluminum hydride in 150 ml. of anhydrous ether. The mixture was heated at 50°C., with stirring, for one and one-half hours. Thereafter, the excess aluminum hydride was decomposed by the addition of water. The ether layer was separated, dried over magnesium sulphate and evaporated to dryness. The residue was 2-(3-aminopropyl)-1-(4-bromophenyl)isoindole.

Similarly, 2-(3-aminopropyl)-1-(2,4-dibromophenyl)isoindole can be synthesised.

Fifteen grams of 10b-(5,6,7,8-tetrahydro-2-naphthyl)-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one were added in portions to a stirred suspension of 4 grams of lithium aluminum hydride and 250 ml. of anhydrous ether. The mixture was stirred and refluxed for two hours, then excess hydride was decomposed by careful addition of water. The ether layer was separated, dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in 50 ml. of ethanol and treated with anhydrous hydrogen chloride. The mixture was cooled and the solid separated

by filtration. After recrystallisation from aqueous ethanol, 2-(3-aminopropyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)isoindole hydrochloride was obtained.

In a similar manner, 2-(3-aminopropyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)isoindole; 2-(3-aminopropyl)-1-(2-trifluoromethylphenyl)isoindole and 2-(3-aminopropyl)-1-furylisoindole can be produced.

Following the procedure immediately above but starting with 10b-benzyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one 2-(3-aminopropyl)-1-benzylisoindole can be obtained.

Similarly, starting with 10b-(2,4-dimethoxyphenyl)-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one, 2-(3-aminopropyl)-1-(2,4-dimethoxyphenyl)isoindole can be obtained.

When the above procedure is employed, and the hereinafter listed pyrimidoisoindolones are reacted with lithium aluminum hydride, the following products are obtained:

15	<i>Starting Material</i>	<i>Product</i>	15
	9-chloro-10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one	2-(3-aminopropyl)-6-chloro-1-phenylisoindole	
	8-methyl-10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one	2-(3-aminopropyl)-5-methyl-1-phenylisoindole	
20	9-ethylamino-10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one	2-(3-aminopropyl)-6-ethylamino-1-phenylisoindole	20
	8,9-dichloro-10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one	2-(3-aminopropyl)-5,6-dichloro-1-phenylisoindole	
25	8,9-dimethoxy-10b-phenyl-1,2,3,4,6,10b-hexahydropyrimido[2,1-a]isoindol-6-one	2-(3-aminopropyl)-5,6-dimethoxy-1-phenylisoindole	25

Following the procedure of Example 1 and catalytically hydrogenating the 2-(3-aminopropyl)isoindoles prepared above 7 to 10, the following 2-(3-aminopropyl)isoindolines can be prepared:

30	2-(3-aminopropyl)-1-(4-bromophenyl)isoindoline;		30
	2-(3-aminopropyl)-1-(2,4-dibromophenyl)isoindoline;		
	2-(3-aminopropyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)isoindoline hydrochloride;		
	2-(3-aminopropyl)-1-(2-trifluoromethylphenyl)isoindoline;		
	2-(3-aminopropyl)-1-furyl isoindoline;		
35	2-(3-aminopropyl)-1-benzylisoindoline;		35
	2-(3-aminopropyl)-1-(2,4-dimethoxyphenyl)isoindoline;		
	2-(3-aminopropyl)-6-chloro-1-phenylisoindoline;		
	2-(3-aminopropyl)-5-methyl-1-phenylisoindoline;		
	2-(3-aminopropyl)-5,6-dichloro-1-phenylisoindoline; and		
	2-(3-aminopropyl)-5,6-dimethoxy-1-phenylisoindoline.		

#### 40 EXAMPLE 6

(For reference purposes)

Following the procedure of Example 5, twenty-five grams of 1-ethyl-9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one were reduced with lithium aluminum hydride to 2-(2-ethylaminoethyl)-1-phenylisoindole and isolated as the hydrochloride, m.p. 200—2°C.

Anal. Calcd for  $C_{18}H_{20}N_2HCl$ : C, 71.86; H, 7.03; N, 9.31; Cl, 11.79. Found: C, 71.74; H, 6.74; N, 9.29; Cl, 11.7.

#### EXAMPLE 7

The procedure of Example 6 can be repeated to convert an appropriate 1-alkyl-tetrahydroimidazoisoindolone to the hereinafter listed 2-[2-(lower alkylamino)ethyl]isoindole:

50	1-(4-chlorophenyl)-2-[2-(ethylamino)ethyl]isoindole hydrochloride (for reference purposes)		50
	6-bromo-2-[2-(butylamino)ethyl]-1-(4-tolyl)isoindole;		
55	2-[2-(methylamino)ethyl]-5-methyl-1-propylisoindole;		55
	5,6-dibromo-1-(4-bromophenyl)-2-[2-(ethylamino)ethyl]isoindole;		
	1-(4-trifluoromethylphenyl)-2-[2-(pentylamino)ethyl]isoindole acetate;		
	2-[2-(methylamino)ethyl]-1-furylisoindole;		
	1-benzyl-2-[2-(ethylamino)ethyl]isoindole;		
60	2-[2-(butylamino)ethyl]-1-(2,4-dimethoxyphenyl)isoindole;		60
	2-[2-(ethylamino)ethyl]-1-(5,6,7,8-tetrahydro-2-naphthyl)isoindole hydrochloride; and		
	2-[2-(butylamino)ethyl]-5,6-dichloro-1-phenylisoindole.		

## EXAMPLE 8

Twenty g. of 9b-(4-chlorophenyl)-1,2,3,9b-tetrahydro-1-(4-tolylsulphonyl)-5H-imidazo[2,1-a]isoindol-5-one were added in portions to a suspension of 7 g. of lithium aluminum hydride in 500 ml. of ether. After refluxing seventeen hours, the mixture was decomposed by careful addition of water. The ether layer was separated and the remaining solid extracted three times with hot ethyl acetate. The organic layers were combined and evaporated to dryness. On recrystallisation from ethanol N-(2-[1-(4-chlorophenyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide, m.p. 142-4°C was obtained.

In a similar manner, 1,2,3,9b-tetrahydro-9b-phenyl-1-(4-tolylsulphonyl)-5H-imidazo[2,1-a]isoindol-5-one is reduced with lithium aluminum hydride to afford N-[2-(1-phenyl-2-isoindolyl)ethyl]-4-toluenesulphonamide, m.p. 112-4°C.

## EXAMPLE 9

Following the procedure of Example 8, and reacting the appropriate 1-(4-tolylsulphonyl)tetrahydroimidazoisoindolone with lithium aluminum hydride in an anhydrous, reaction-inert, organic solvent at temperatures within the range of 30°C to 80°C for a period of one to seventeen hours, the following isoindolyltoluenesulphonamides can be produced:

N-(2-[5-bromo-1-(4-tolyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide;  
N-[2-(4-methyl-1-propyl-2-isoindolyl)ethyl]-4-toluenesulphonamide;  
N-(2-[4,5-dibromo-1-(4-bromophenyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide;  
N-(2-[1-(3,4-dichlorophenyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide;  
N-(2-[1-(4-trifluoromethylphenyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide;  
N-[2-(4,5-dimethoxy-1-phenyl-2-isoindolyl)ethyl]-4-toluenesulphonamide;  
and N-[2-(1-furyl-2-isoindolyl)ethyl]-4-toluenesulphonamide.

In a similar manner, by following the aforesaid procedure and reacting appropriate 1-(4-tolylsulphonyl)hexahydropyrimidoisoindolones with lithium aluminum hydride the following isoindolyltoluenesulphonamides are produced:

N-(3-[6-bromo-1-(4-tolyl)-2-isoindolyl]propyl)-4-toluenesulphonamide;  
N-[3-(4-methyl-1-propyl-2-isoindolyl)propyl]-4-toluenesulphonamide;  
N-(3-[4,5-dibromo-1-(4-bromophenyl)-2-isoindolyl]propyl)-4-toluenesulphonamide;  
N-(3-[1-(3,4-dichlorophenyl)-2-isoindolyl]propyl)-4-toluenesulphonamide;  
N-[3-(5,6-dimethoxy-1-phenyl-2-isoindolyl)propyl]-4-toluenesulphonamide;  
N-(3-[1-(4-trifluoromethylphenyl)-2-isoindolyl]propyl)-4-toluenesulphonamide;  
and N-[3-(1-furyl-2-isoindolyl)propyl]-4-toluenesulphonamide.

## EXAMPLE 10

Forty grams of 10b-(4-chlorophenyl)-1,2,3,4,6,10b-hexahydro-1-(4-tolylsulphonyl)pyrimido[2,1-a]isoindol-6-one were added in portions to a suspension of 14 g. of lithium aluminum hydride in 1000 ml. of ether. After refluxing ten hours, the mixture was decomposed by careful addition of water. The ether layer was separated and the remaining solid extracted three times with hot ethyl acetate. The organic layers were combined and evaporated to dryness. On recrystallisation from ethanol N-(3-[1-(4-chlorophenyl)-2-isoindolyl]propyl)-4-toluenesulphonamide, m.p. 111-3°C was obtained.

Anal. Calcd. for  $C_{24}H_{28}N_2SO_2Cl$ : C, 65.36; H, 5.71; N, 6.35; Cl, 8.04; S, 7.27. Found: C, 65.29; H, 5.69; N, 6.03; Cl, 8.0; S, 7.3.

## EXAMPLE 11

(a) Fifteen grams of  $\alpha$ -(2-aminoethylamino)- $\alpha$ -phenyl-2-toluic acid, 4 g. of 10% palladium on charcoal and 200 ml. of ethanol were shaken with hydrogen at an initial pressure of 43 p.s.i. After eight hours, the catalyst was separated by filtration and the filtrate evaporated to dryness. The residue was dissolved in ethanol and saturated with hydrogen chloride. After cooling, the precipitated solid was separated by filtration. On recrystallisation from alcohol-acetone there was obtained 2-(2-aminoethyl)-3-phenylphthalimidine hydrochloride, m.p. 262°C.

(b) This compound was converted to the free base and 12 grams thereof were added to a stirred suspension of 6 g. of lithium aluminum hydride in 500 ml. of anhydrous ether. The mixture was stirred and refluxed for fifteen hours before being decomposed by the careful addition of water. The ether layer was separated, dried over magnesium



sulphate and evaporated to dryness. The residue was dissolved in absolute ethanol and saturated with hydrogen chloride. The solid was separated and recrystallised from alcohol. On drying 2-(2-aminoethyl)-1-phenylisoindoline hydrochloride.

#### EXAMPLE 12

- 5 (a) Following the procedure of Example 11(a)  $\alpha$ -(2-aminoethylamino)- $\alpha$ -(4-chlorophenyl)-2-toluic acid was converted to 2-(2-aminoethyl)-3-(4-chlorophenyl)phthalimidine hydrochloride, m.p. 305°C (dec). 5
- (b) This compound can be converted to 2-(2-aminoethyl)-1-(4-chlorophenyl)isoindoline hydrochloride m.p. 220—223°C, following the procedure of Example 11(b).
- 10 Anal. Calcd. for  $C_{16}H_{17}N_2Cl$ : C, 62.15; H, 5.87; N, 9.06; Cl, 22.93. Found: C, 61.76; H, 6.09; N, 9.44; Cl, 22.70. 10

#### EXAMPLE 13

- 15 (a) Following the procedure of Example 11(a)  $\alpha$ -(4-aminobutylamino)- $\alpha$ -(4-chlorophenyl)-2-toluic acid, m.p. 262°C (dec) was converted to 2-(4-aminobutyl)-3-(4-chlorophenyl)phthalimidine hydrochloride, m.p. 175—177°C. 15
- (b) This compound can be converted to 2-(4-aminobutyl)-1-(4-chlorophenyl)isoindoline dihydrochloride m.p. 162—5°C following the procedure of Example 11(b).

#### EXAMPLE 14

- 20 (a) Following the procedure of Example 11(a),  $\alpha$ -(6-aminoethylamino)- $\alpha$ -(4-chlorophenyl)-2-toluic acid, m.p. 225°C (Dec) can be converted to 2-(6-aminoethyl)-3-(4-chlorophenyl)phthalimidine hydrochloride. 20
- In a similar manner, 2-(3-aminopropyl)-3-phenylphthalimidine, and 2-(4-aminobutyl)-3-(4-bromophenyl)phthalimidine can be prepared.
- 25 (b) Following the procedure of Example 11(b), these three compounds can be reduced to 2-(6-aminoethyl)-1-(4-chlorophenyl)isoindoline, 2-(3-aminopropyl)-1-phenyl-isoindoline and 2-(4-aminobutyl)-1-(4-bromophenyl)isoindoline respectively. 25

#### EXAMPLE 15

- 30 Thirty grams of  $\alpha$ -[(2-aminoethyl)imino]-4-bromo- $\alpha$ -(4-tolyl)-2-toluic acid, 8g. of 10% palladium on charcoal and 400 ml. of ethanol were shaken with hydrogen at an initial pressure of 45 p.s.i. After ten hours, the catalyst was separated by filtration and the filtrate evaporated to dryness. In this manner, there was obtained 2-(2-aminoethyl)-6-bromo-3-(4-tolyl)phthalimidine. 30
- 35 Six grams of the above prepared phthalimidine were added to a stirred suspension of 6 g. of lithium aluminum hydride in 500 ml. of anhydrous ether. The mixture was stirred and refluxed for twelve hours and then decomposed with water. The ether layer was separated, dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in absolute ethanol and saturated with hydrogen chloride. The solid was separated and recrystallised from alcohol to afford 2-(2-aminoethyl)-5-bromo-1-(4-tolyl)isoindoline hydrochloride. 35

#### EXAMPLE 16

- 40 The procedure of Example 15 can be repeated to convert the hereinafter listed  $\alpha$ -imino-2-toluic acids to their corresponding 2-[amino(lower)alkyl]phthalimidines which are then reduced to form appropriate isoindolines: 40

$\alpha$ -IMINO-2-TOLUIC ACIDS	2-[AMINO(LOWER)ALKYL] PHTHALIMIDINES	ISOINDOLINES
$\alpha$ -[(2-aminoethyl) imino]-4,5-dibromo- $\alpha$ -phenyl-2-toluic acid	2-(2-aminoethyl)-5,6-dibromo-3-phenylphthalimidine	2-(2-aminoethyl)-5,6-dibromo-1-phenylisoindoline hydrochloride
$\alpha$ -[(3-aminopropyl) imino]- $\alpha$ -(3,4-dichlorophenyl)-2-toluic acid	2-(3-aminopropyl)-3-(3,4-dichlorophenyl)phthalimidine	2-(3-aminopropyl)-1-(3,4-dichlorophenyl)isoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]- $\alpha$ -(5,6,7,8-tetrahydro-2-naphthyl)-2-toluic acid	2-(2-aminoethyl)-3-(5,6,7,8-tetrahydro-naphthyl)phthalimidine	2-(2-aminoethyl)-1-(5,6,7,8-tetrahydro-2-naphthyl)isoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]- $\alpha$ -(4-trifluoromethylphenyl)-2-toluic acid	2-(2-aminoethyl)-3-(4-trifluoromethylphenyl)phthalimidine	2-(2-aminoethyl)-1-(4-trifluoromethylphenyl)isoindoline hydrochloride
$\alpha$ -[(5-aminopentyl) imino]- $\alpha$ -pyridyl-2-toluic acid	2-(5-aminopentyl)-3-pyridylphthalimidine	2-(5-aminopentyl)-1-pyridylisoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]- $\alpha$ -thienyl-2-toluic acid	2-(2-aminoethyl)-3-thienylphthalimidine	2-(2-aminoethyl)-3-thienylisoindoline hydrobromide
$\alpha$ -[(2-aminoethyl) imino]-5-chloro- $\alpha$ -phenyl-2-toluic acid	2-(2-aminoethyl)-5-chloro-3-phenylphthalimidine	2-(2-aminoethyl)-6-chloro-1-phenylisoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]- $\alpha$ -(2,4-dimethoxyphenyl)-2-toluic acid	2-(2-aminoethyl)-3-(2,4-dimethoxyphenyl)phthalimidine	2-(2-aminoethyl)-1-(2,4-dimethoxyphenyl)isoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]-4-ethyl- $\alpha$ -phenyl-2-toluic acid	2-(2-aminoethyl)-6-ethyl-3-phenylphthalimidine	2-(2-aminoethyl)-5-ethyl-1-phenylisoindoline hydrochloride
$\alpha$ -[(4-aminobutyl) imino]-5-ethyl-amino- $\alpha$ -phenyl-2-toluic acid	2-(4-aminobutyl)-5-ethylamino-3-phenylphthalimidine	2-(4-aminobutyl)-6-ethylamino-1-phenylisoindoline hydrochloride
$\alpha$ -[(2-aminoethyl) imino]- $\alpha$ -(2-furyl)-2-toluic acid	2-(2-aminoethyl)-3-(2-furyl)phthalimidine	2-(2-aminoethyl)-1-(2-furyl)isoindoline hydrochloride
$\alpha$ -[(6-aminohexyl) imino]- $\alpha$ -(4-chlorophenyl)-2-toluic acid	2-(6-aminohexyl)-3-(4-chlorophenyl)phthalimidine	2-(6-aminohexyl)-1-(4-chlorophenyl)isoindoline hydrochloride

## EXAMPLE 17

- (a) A mixture of 60 g. of 9b-phenyl-1,2,3,9b-tetrahydro-5H-imidazo[2,1-a]isoindol-5-one, 60 g. of *p*-toluenesulphonyl chloride and 250 ml. of pyridine was refluxed for sixteen hours. The solution was evaporated to a solid residue. On recrystallisation from 95% ethanol, there was obtained 9b-phenyl-1,2,3,9b-tetrahydro-1-(*p*-tolylsulphonyl)-5H-imidazo[2,1-a]isoindol-5-one, m.p. 158—160°C.
- (b) A mixture of 20 g. of toluenesulphonyl derivative from above, 5 g. of 10% palladium on charcoal and 250 ml. of ethanol were shaken with hydrogen at an initial pressure of 39 p.s.i. After 20 hours, the catalyst was separated and the filtrate evaporated to dryness. After recrystallisation from ethanol N-(2-[3-phenyl-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide ethanolate, m.p. 96—8°C was obtained.

## EXAMPLE 18

- (a) A mixture of 2 g. of 2-(2-aminoethyl)-3-phenyl-phthalimidine hydrochloride, 2 g. of *p*-toluenesulphonyl chloride and 25 ml. of pyridine was refluxed two hours. The solution was evaporated to dryness and the residue is recrystallised from 95% ethanol to obtain N-(2-[3-phenyl-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide ethanolate, m.p. 96—8°C.
- (b) Six grams of N-(2-[3-phenyl-2-phthalimidinyl]ethyl)-*p*-toluenesulphonamide ethanolate were added to a stirred suspension of 6 g. of lithium aluminium hydride in 500 ml. of anhydrous ether. The mixture was stirred and refluxed for twelve hours and then diluted with water. The ether layer was separated, dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in absolute ethanol and saturated with hydrogen chloride. The solid was separated and recrystallised from alcohol to afford N-(2-[1-phenyl-2-isoindolinyl]ethyl)-*p*-toluenesulphonamide.
- In a similar manner, the following compounds can be prepared:
- N-(2-[1-(3,4-dimethylphenyl)-2-isoindolinyl]ethyl)-*p*-toluenesulphonamide;  
 N-(2-[5,6-dimethyl-1-phenyl-2-isoindolinyl]ethyl)-*p*-toluenesulphonamide;  
 N-(2-[6-ethoxy-1-phenyl-2-isoindolinyl]ethyl)-*p*-toluenesulphonamide; and  
 N-(2-[1-(3,4-dibromophenyl)-2-isoindolinyl]ethyl)-*p*-toluenesulphonamide.

## EXAMPLE 19

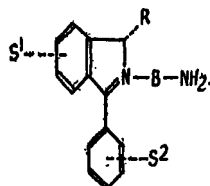
(For reference purposes)

- Six grams of the 2-(2-aminoethyl)-3-(3,5-diethoxyphenyl)-phthalimidine prepared following the procedure of Example 11(a) were added to a stirred suspension of 6 g. of lithium aluminium hydride in 500 ml. of anhydrous ether. The mixture was stirred and refluxed for twelve hours and then diluted with water. The ether layer was separated, dried over magnesium sulphate and evaporated to dryness. The residue was dissolved in absolute ethanol and saturated with hydrogen chloride. The solid was separated and recrystallised from alcohol to afford 2-(2-aminoethyl)-1-(3,5-diethoxyphenyl)isoindoline hydrochloride.
- In the same manner, 2-(2-aminoethyl)-5,6-diethyl-1-phenylisoindoline hydrochloride and 2-(2-aminoethyl)-5,6-diethoxy-1-phenylisoindoline hydrochloride can be prepared.

## EXAMPLE 20

- The hydrochloride salt of 2-(2-ethylaminoethyl)-1-phenylisoindole (prepared according to Example 6) could be prepared by admixing an ethanolic solution of this compound with an equivalent amount of anhydrous hydrogen chloride and, thereafter evaporating the aqueous solvent under vacuum.
- Other acid addition salts of the isoindole and isoindoline compounds of the above Examples can be prepared by the same procedure employing hydrobromic acid, hydroiodic acid, nitric acid, sulphuric acid, phosphoric acid, acetic acid, lactic acid, citric acid, tartaric acid, maleic acid and gluconic acid.

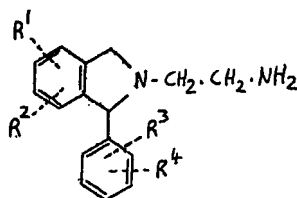
Specification No. 1,097,168 claims compounds of the general formula



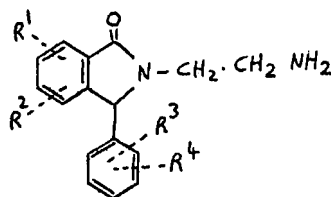
- wherein S<sup>1</sup> and S<sup>2</sup> each represent substitution by one or more halo, lower-alkyl, lower-alkoxy, hydroxy, sulphonyl, sulphinyl, sulphonyl, lower-alkylmercapto, lower alkyl

amino, di(lower alkyl)amino, acylamino and/or trifluoromethyl substituents, R represents a lower-alkyl group and B represents a straight chain or branched chain alkylene group containing from 2 to 12 carbon atoms in which part or all of the carbon atoms may form a 3- to 7- membered carbocyclic ring and wherein the broken lines denote that the R group and the S<sup>1</sup> and S<sup>2</sup> substitution is optional, and acid addition salts thereof. We make no claim herein to compounds claimed in Specification No. 1,097,168.

Specification No. 1,144,060 claims, in Claim 16 thereof, in effect, a process for the preparation of isoindolines having the general formula:

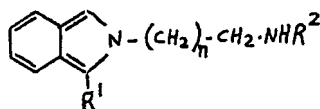


and their pharmaceutically acceptable acid addition salts by reducing a compound having the general formula:

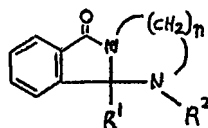


or its pharmaceutically acceptable acid addition salt, with an alkali-metal aluminium hydride complex and if desired converting the reduction product into a pharmaceutically acceptable acid addition salt; wherein in the above formulae R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> indicate optional halogen, trifluoromethyl, hydroxy, amino, loweralkyl, loweralkoxy, loweralkylamino or diloweralkylamino substituents. We make no claim herein to the process claimed in Claim 16 or Specification No. 1,144,060.

Specification No. 1,162,835 claims in Claim 6 thereof, in effect, compounds having the general formula:



in which R<sup>1</sup> is phenyl or 4-chlorophenyl, n=1 or 2 and R<sup>2</sup> is hydrogen or an alkyl radical having 1 to 4 carbon atoms when n is 2 or an alkyl radical only having 1 to 4 carbon atoms when n is 1, and their acid addition salts. Claim 8 claims the compound 1-phenyl-2(2'-N-ethylaminoethyl-1'-)-isoindole. Claim 3 claims the preparation of such compounds and their acid addition salts from those of general formula:



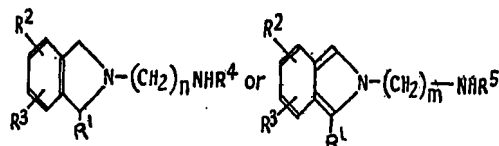
where R<sup>1</sup>, R<sup>2</sup> and n have the above significance by reduction with lithium aluminium hydride and optional conversion into an acid addition salt; and Claim 10 claims pharmaceutical compositions containing a physiologically acceptable inert carrier and a compound according, inter alia, to Claim 6 or Claim 8. We make no claim herein

to the compounds claimed in Claim 6 and 8 of specification No. 1,162,835, to the process claimed in its Claim 3 or to pharmaceutical compositions claimed in Claim 10.

Subject to the foregoing disclaimers

WHAT WE CLAIM IS:—

5 1. A compound of the general formula:



or an addition salt thereof with a pharmaceutically acceptable acid, in which formulae, R<sup>1</sup> is lower alkyl, phenyl, phen(lower)alkyl, monohalophenyl, dihalophenyl, mono(lower)alkylphenyl, di(lower)alkylphenyl, trifluoromethylphenyl, mono(lower)alkoxyphenyl, di(lower)alkoxyphenyl, thienyl, pyridyl, furyl or 5, 6, 7, 8-tetrahydro-2-naphthyl; R<sup>2</sup> and R<sup>3</sup> are the same and are hydrogen, halogen, lower alkyl or lower alkoxy; or R<sup>2</sup> is hydrogen and R<sup>3</sup> is amino, loweralkylamino, halogen, lower alkyl or lower alkoxy; R<sup>4</sup> is hydrogen or toluenesulphonyl; R<sup>5</sup> is lower alkyl, m is 2 or 3; n is an integer from 2 to 7; and the term "lower" means that the radical contains up to 6 carbon atoms.

2. Compounds as claimed in Claim 1, wherein R<sup>1</sup> is phenyl, monohalophenyl, dihalophenyl, trifluoromethylphenyl, 5, 6, 7, 8-tetrahydro-2-naphthyl, tolyl or diloweralkoxyphenyl; R<sup>2</sup> is hydrogen and R<sup>3</sup> is hydrogen or halogen.

3. Compounds as claimed in Claim 2, wherein R<sup>1</sup> is phenyl, monochlorophenyl, dichlorophenyl, trifluoromethylphenyl, 5, 6, 7, 8-tetrahydro-2-naphthyl or tolyl; R<sup>2</sup> is hydrogen and R<sup>3</sup> is hydrogen or bromine.

4. N-(2-[1-(4-chlorophenyl)-2-isoindolyl]ethyl)-4-toluenesulphonamide.

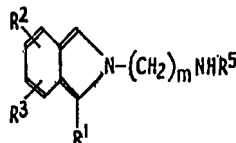
5. N-[2-(1-phenyl-2-isoindolyl)ethyl]-4-toluenesulphonamide.

6. N-(3-[1-(4-chlorophenyl)-2-isoindolyl]propyl)-4-toluenesulphonamide.

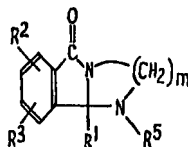
7. N-(2-[1-phenyl-2-isoindolyl]ethyl)-p-toluenesulphonamide.

8. The addition salts, with pharmaceutically acceptable acids, of the compounds claimed in any of Claims 2 to 7.

9. A process for the preparation of compounds of the general formula

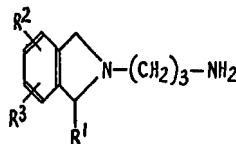


30 where R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, m and R<sup>5</sup> have the meanings defined in Claim 1 which comprises reacting a compound of the general formula



(where R<sup>1</sup>, R<sup>2</sup>, R<sup>3</sup>, m and R<sup>5</sup> have the meanings defined above) with lithium aluminium hydride.

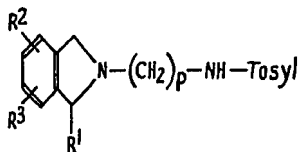
35 10. A process for the preparation of a compound of the general formula



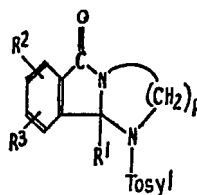
(where  $R^1$ ,  $R^2$  and  $R^3$  have the meanings defined in Claim 22) which comprised catalytically reducing the corresponding isoindole.

11. A process as claimed in Claim 10, wherein reduction is effected with hydrogen in the presence of palladium/carbon.

5 12. A process for the preparation of a compound of the general formula



(in which  $R^1$ ,  $R^2$  and  $R^3$  have the meanings defined in Claim 1  $p$  is 2 or 3 and Tosyl is a toluenesulphonyl radical), which comprises reducing a compound of the general formula

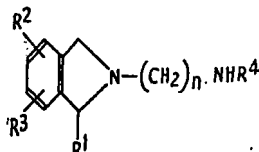


10

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(where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $p$  and Tosyl have the meanings defined above) with lithium aluminium hydride.

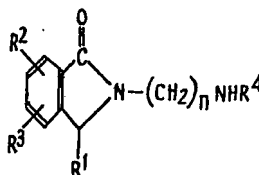
13. A process for the preparation of a compound of the general formula



15

(where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $n$  have the meanings defined in Claim 1), which comprises reducing a phthalimidine of the general formula

15

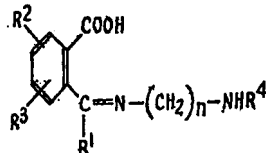


20

(where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $n$  have the meanings defined above) with lithium aluminium hydride.

14. A process as claimed in Claim 13, wherein the phthalimidine is prepared by reducing an  $\alpha$ -imino-2-toluic acid of the general formula

20



25

(where  $R^1$ ,  $R^2$ ,  $R^3$ ,  $R^4$  and  $n$  have the meanings defined in Claim 15) with hydrogen in the presence of palladium/carbon.

15. A process as claimed in Claim 9, wherein the reaction is carried out in an anhydrous, reaction-inert organic solvent at a temperature in the range of from 30 to 80°C.

25

16. A process as claimed in Claim 15, wherein the reaction is carried out in anhydrous ether under reflux.

17. A process as claimed in any of Claims 9 to 16 substantially as described with reference to the Examples.

18. Compounds as claimed in Claim 1, when prepared by the process claimed in any of Claims 9 to 17.

5 19. A pharmaceutical composition comprising a compound as claimed in any of Claims 1 to 8 or 18 and a pharmaceutically acceptable carrier. 5

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